AstraZeneca

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November 8, 1999

Dockets Management Branch (HFA- 305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

Docket No. 97D - 0433
Comments on Draft Guidance for Industry: "Average, Population and Individual Approaches to Establishing Bioequivalence"

Dear Madam/Sir:

Reference is made to FDA's draft guidance as described above which was published in the September 8, 1999 Federal Register.

AstraZeneca LP has reviewed this guidance and our comments are attached.

If you have any questions regarding these comments, please do not hesitate to contact me. Thank you for your consideration.

Sincerely,

Elizabeth Fenna
Sr. Regulatory Project Manager
Regulatory Affairs

97D-0433

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AstraZeneca comments on FDA Guidance Document. Guidance for Industry: Average Population and Individual Approaches to Establishing Bioequivalence.

Section/ Page number	Comment
General	We believe that international harmonization is very important. We are concerned that using new approaches to establish bioequivalence may complicate this harmonization. Preferably, the same analysis should be accepted all over the world. It is therefore desirable that any new bioequivalence concepts be reviewed and approved by ICH.
General	What are the consequences of a trial that does not demonstrate Individual Bioequivalence (IBE)? What if there is substantial patient*formulation interaction? Please clarify.
I/1	The Introduction states that "Information about when to use these criteria in BE studies is provided in this guidance ...". We found that this information is difficult to find and not very specific. Please clarify.
II.B/3	There is reference to the limitations of the Average Bioequivalence (BE) approach. We believe that there is little or no evidence that Population Bioequivalence (PBE) or IBE criteria would result in lower patient risk than BE criteria. In addition, there is also little or no evidence that has demonstrated significant problems with switching to/from generics. If this is the case, what problem will IBE solve? This is particularly important when the suggested approach to demonstrate IBE increases the complexity of the trial with regard to understanding, trial conduct and statistical analysis.
II.B/3 Footnote	A key question here is which degree of variation is clinically relevant? What is the rationale for the old BE interval of 80%-125%? When reading the draft guidelines (e.g. page 3), one gets the impression that the standard BE interval for Cmax is also 80%-125%. There are strong reasons to have a wider interval (and larger thetas) for Cmax for most drugs.

II.B/4 The last sentence of II.B states "...the prescriber and patient should be assured that the newly administered drug product will yield comparable safety and efficacy to that of the product for which it is being substituted."
We agree with this statement. However, how does IBE provide this? It is realized that the whole aim of bioequivalence is to demonstrate it, and then use the assumption that bioequivalence implies equivalence in safety and efficacy. Often, the PK-PD relationship is ill defined (or not defined at all). When this is the case, IBE does not seem relevant.

III/4 The mixed-effects structure described for log-transformed data is probably reasonable in many situations. However, the associated distributional (normality) assumptions concerning variability components may be much more questionable.

Nonnormality is less crucial for the BE approach than for the PBE and IBE approaches described. The reason is that the BE approach concerns decisions/inferences about means (which are robust against departures from normality), whereas the PBE and IBE approaches concern decisions/inferences that, to a much larger extent, involve variance components (which are very nonrobust against departures from normality). The PBE and IBE approaches are thus much more assumption dependent, which we believe, is inappropriate in a regulatory context.

For example, the way in which subjects are included (through explicit/implicit selection mechanisms) obviously influences the shape/spread of the between-subject variability component. This variability component influences the proposed PBE criteria, and the proposed IBE criteria (through the subject-by formulation interaction, see Equation 1), so PBE and IBE decisions/inferences may be influenced in nonnegligible manners and in unexpected directions. Moreover, one can hardly expect that a log-transformation should help with respect to this between-subject component, even if such a transformation may help with respect to other variability components.

III/4 We believe there is an error in equation 1: σ_D^2 and not σ^2.

IV It is not clear whether the IBE criterion is superior to the BE criterion or the PBE criterion for assessment of drug interchangeability. I.e. it is not clear whether or not IBE implies PBE and PBE implies BE under aggregate criteria. Please clarify.

IV.B,C/6-8 The PBE and IBE criteria have certain weaknesses due to the fact that they are based on aggregate measures, e.g.: (a) arbitrariness in the implicit weighting of the components it involves, and (b) arbitrariness in the way these components are allowed to compensate each other.

It should be mentioned that the proposed PBE and IBE criteria are possible/acceptable, but that other approaches (with essentially the same aims) may also be acceptable. For example, approaches based on showing equivalence for relevant (less aggregated functions of) components should be mentioned as a possibility.

IV.B,C/6-8 We suggest combining Equations 4-5 (and similarly Equations 6-7) into the relevant Single Equivalence condition actually specified in the text after the equations: simply set the denominator equal to max (Ref-Variance, Specified Constant) in one of the two equations.

V.A/8 Trials having three or four periods will take a longer time to perform than the now commonly used two period design. A longer trial also means that the risk of dropouts increases. The problem most affects drugs with a long elimination half-life. For steady state trials, it might be considered to skip the washout period in order to decrease study time. (For ethical reasons, washout periods are sometimes not possible.) Pharmacokinetic reasoning could perhaps be used instead of statistical modeling of carry-over effects. For a drug with ordinary kinetics, approximate steady state will be achieved after, say, five half-lives, irrespective of the plasma concentration at the start. If the length of the treatment periods is more than five half-lives, the carry-over effect is therefore likely to be negligible even without a washout period.

V.B/9 A small problem concerning universal applicability of one trial is the requirement of Section V.B. to have a 'reasonable balance of ... racial groups'. This advice should probably not be interpreted as contraindicating studies in countries or areas with a homogeneous population. In some cases, it could be useful to perform one study in two or more countries to achieve higher heterogeneity.

V.B/9	With the exception of average BE, the theory relies on using a mixed effects model. The section on study population on this page discusses some of the practical ramifications of this assumption, but doesn't seem to cover the use of patients particularly clearly. Is BE proven in healthy volunteers (from an admittedly 'as heterogeneous population as possible') an indication of BE in all patient groups?
V.C/9	Please clarify that at least 12 subjects should be "evaluable" rather than "included".
V.C/9-10	We recommend that in the third sentence of Section C, the two words "should" and "because" be replaced by "may" and "if". Developments in this context will certainly be made in the future, and good approximations may become available. Also some statement like "a variety of simulation techniques may be used" might help, as currently simulation is a "wide-open" field.
VI.A.1/10	Log transformations – we recommend that it be noted that it doesn't matter which method you use, as it's only a tool for getting to the geometric means and ratios.
VI.A.1/10	The phrase 'normality of data' can be misleading - it implies that your response data is supposed to be normally distributed, as opposed to your error distribution.
VI.A.1/10	In view of the assumption dependence of the proposed PBE and IBE approaches, one should not overly discourage investigations of whether underlying assumptions are reasonable. For example, it could be mentioned that the log-transformation is currently acceptable even with some departure from normality. Of course this leads to some arbitrariness, but this seems unavoidable. We believe that formal tests of normality do not provide good answers as to whether data are sufficiently normal; for this reason, we believe that such formal testing should be discouraged.
VI.A.2/10-11	For log-transformed data only geometric mean and CV needs presenting where CV is defined as CV=srqt(exp(σ^2)-1)) and where σ is standard deviation on log scale. Alternatively σ could be presented instead of CV.

VI.B.1.d/12 For average bioequivalence, it is perhaps better to say that one should assume equal variances. The analysis will be rather robust even if this isn't true. If that assumption is not made, there are different approximate solutions but no obvious standard.

VI.B.2-3/12-14 For the proposed PBE approach (as well as the IBE approach) it is stated that: "To obtain the 95% upper confidence bound for the criterion, intervals based on validated approaches can be used".
It seems that this refers to each of the two component criteria in Equations 4-5 (as well as each of the two component criteria in Equations 6-7), that is, the upper 95% upper bound for: (a) the reference scaled criterion, and (b) the constant scaled criterion.

However, one should also consider or investigate the consequences of the proposal to switch between (a) and (b) depending on whether the estimated Reference variance is larger than a specified constant or not. The dependence (through the estimated Reference variance) between the random switch and the selected confidence bound does not seem to have been taken into account. The influence of this dependence may be nonnegligible, particularly with small sample sizes. What is the probability of making an erroneous equivalence decision (unconditionally; and conditionally on the switch outcome, which is observable) with the proposed procedure, how does this probability depend on the magnitude of the underlying variance component(s), and is this probability bounded from above by 5% or by something else?

Depending on the answer to these questions, the proposed approach may have to be modified.

VI.B.3/14 The guideline mentions discussions with CDER about analysis before application. It should be made clear that it is important that the sponsor states clearly in the protocol how the data will be analysed.

VII.A/14 It is not understood why Section VII.A. states that combination of data from different sites should be problematic. Please explain this.

VII.A/14	We recommend that sequential designs be included in this guidance. For average bioequivalence, standard sequential designs can easily be used. This should be possible to do without consultation. For individual and population BE, some research about sequential methods is probably needed. We recommend that CDER provide general advice on how p-value corrections may be done at a later date.
VII.D	The discontinuity mentioned here reflects an obviously disturbing behaviour of the proposed procedure based on the switch. As commented on re section VI.B.2-3, somewhat more basic problems have to be investigated in this context.
AppA/A-2	Please provide a justification for the maximum allowable PDR and IDR of 1.25.
AppA/A-3,4	Please provide a justification for ε_p and ε_l values.
AppC/C-4	The guideline states that the power should be 80% or 90%. We believe that the sponsor should decide the power based upon many critical factors.
AppC/C-4,5	Several columns in the tables have the same heading of σ. Please clarify this.
AppF-H	These appendices are not clear. There are many equations, formulae etc. that are not explained or justified. We recommend that this section be clarified.
AppF-H	There may be more suggestions for statistical analyses published in literature at a future time. It would therefore be useful if CDER indicates on a regular basis which statistical method(s) are acceptable.

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